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Peripheral Neural Circuitry in Cough

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Abstract

Cough is a reflex that serves to protect the airways. Excessive or chronic coughing is a major health issue that is poorly controlled by current therapeutics. Significant effort has been made to understand the mechanisms underlying the cough reflex. The focus of this review is the evidence supporting the role of specific airway sensory nerve (afferent) populations in the initiation and modulation of the cough reflex in health and disease.

Introduction

Cough is an airway reflex in guinea pigs and larger mammals that serves to expel unwanted matter from the airways. Stimuli induce cough by activating afferent (sensory) nerves innervating the airways. These signals are transmitted centrally via the vagus nerve, where they synapse with networks in the brainstem (e.g. nucleus tractus solitarius (nTS)). Such networks coordinate the activation of motor output (e.g. phrenic, intercostal and recurrent laryngeal nerves (RLN)) and the ultimate expression of cough. The focus of this review will be the afferent nerves involved in cough: their characterization, activation and function.

Key to the understanding of afferents involved in cough is the use of specific stimuli to evoke cough experimentally. In anesthetized animals cough is evoked by mechanical stimulation (i.e. punctate) of the larynx, trachea and main bronchi [1, 2]. This cough rapidly adapts to continued pressure, although repeated stimulation will evoke further coughs. Application of water and citric acid to these airways also evokes cough in anesthetized animals [3–5]. Interestingly, cough can be evoked by many other stimuli in conscious animals (but not in anesthetized animals). Thus inhalation of irritants such as bradykinin, capsaicin, cinnamaldehyde and acrolein evokes cough [1, 6–, 10, 11*], as can bronchoconstricting agents [12–14]. Regardless of which receptors are involved, afferent activation depends on the gating of membrane ion channels at the airway afferent terminal.

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Conflict of Interest
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This leads to nerve depolarization (graded potential), which triggers the activation of voltage-gated sodium channels (Na_v) and the initiation of action potentials, that conduct towards the brainstem [15, 16*].

Afferent innervation of the larynx, trachea, bronchi and intrapulmonary airways is largely supplied by the vagus nerve and its branches (e.g. RLN and superior laryngeal nerve (SLN)). The vagal ganglia comprises of the nodose and jugular ganglia, whose afferent neurons arise from distinct embryological sources (placodes and neural crest, respectively) [17]. Such differences manifest themselves in differential protein expression and functionality [18, 19]. Airway afferents are not homogenous and numerous subtypes have been determined. Details of these subtypes can be found elsewhere [5, 15, 20, 21], here we will focus on two important groups: the nodose A δ fibers innervating the extrapulmonary airways and the vagal C fibers innervating throughout the airways. Both groups can be considered 'nociceptive' – afferents that do not respond to eupneic breathing and other 'normal' events, but which respond specifically to stimuli that can be considered noxious (or potentially noxious) [22].

Nodose A δ activation

Highly arborized nerve terminals are found innervating the smooth muscle layer of the extrapulmonary airways [2, 23]. These are the peripheral terminals of myelinated afferents originating exclusively from the nodose ganglion. Electrophysiological recordings indicate conduction velocities of approximately 5m/s (A δ fibers) [24, 25]. These afferents are exquisitely sensitive to punctate mechanical force, but not stretch. Acidic solutions, hypotonic and hypertonic solutions also activate extrapulmonary nodose A δ fiber terminals [24, 26]. Responses to continued punctate force or acidic solutions rapidly ceases (adaptation) [27]. A δ fibers in healthy animals are completely insensitive to bradykinin and capsaicin (selective agonist of transient receptor potential vanilloid 1 (TRPV1)) [1, 24], due to a lack of TRPV1 expression [28**].

Nodose A δ fibers innervating the trachea and larynx are carried by the RLN branch of the vagus [24]. Bilateral transection of the RLN interrupts A δ fiber signaling [2, 24] and cough evoked in anesthetized guinea pigs by stimulation of the trachea [1, 2, 29]. SLN transection had no effect on A δ fiber signaling/cough. Recently, a more specific approach has indicated the contribution of nodose A δ fibers to cough [30**]. Na_v1.7, a vagal voltage-gated sodium channel, has been shown to be critical for action potential discharge in vagal afferents innervating the airways [31]. Using in vivo adeno-associated virus (AAV) delivery specifically to nodose neurons (jugular was not transfected) of shRNA targeted against Na_v1.7, the overall electrical activity of nodose afferents was significantly reduced (jugular afferents were not reduced) [30**]. In these studies punctate stimulation (under anesthesia) of the trachea evoked 11 ± 3 coughs in control guinea pigs but only 2 ± 1 coughs in nodose Na_v1.7 knockdown guinea pigs. Breathing rates were not different between the groups.

The receptors responsible for A δ fiber activation have not been definitively determined. Acid activates both TRPV1 and a family of proteins termed the Acid-Sensing Ion Channels (ASIC) in sensory neurons. However, TRPV1 is not expressed in A δ fibers and selective

TRPV1 inhibitors have no effect on acid-induced A δ fiber activation [26]. The mRNA for multiple ASICs have been found in nodose neurons [32*], but specific studies in airway afferents are lacking. Numerous candidates have been proposed for mediating mechanical-induced sensory nerve activation including EnaC, TRPV4, TRPA1, and Piezo [15, 33–36], but so far no definitive determinations have been made.

Characterizations of A δ fiber terminals and their nodose soma suggest that these neurons represent a biochemically distinct neuronal subset [24, 37]. These neurons express neurofilament, neuronal nitric oxide synthase and vGlut1 and vGlut2 (transport glutamate into excitatory vesicles) but do not express substance P, CGRP or somatostatin (nociceptor neuropeptides). Interestingly, these fibers express the α_3 subunit of the Na-K-ATPase pump, which is not found elsewhere within the trachea [2, 37]. Ouabain, at concentrations that preferentially block α_3 subunit, inhibited the activation of tracheal A δ fibers and inhibited cough evoked by tracheal stimulation in anesthetized guinea pigs [2]. Ouabain had no effect on basal breathing rates or on citric acid-induced apneas, suggesting a selective inhibition of tracheal A δ fiber afferents.

Vagal C fiber activation

The vast majority of airway afferents are unmyelinated and conduct action potentials at 0.3–1.5 m/s (C fibers) [18, 38, 39]. C fibers terminate in unstructured endings throughout the mucosa and submucosa of the airways [2, 23, 40]. C fibers are polymodal sensors of noxious stimuli [18, 41–43], due to their characteristic expression of specific receptors for noxious stimuli. The hallmark of C fiber nociceptive afferents is sensitivity to capsaicin due to the expression of TRPV1 in nociceptors [44]. Capsaicin activates airway C fibers [18, 24, 38, 42, 43], and this is abolished by selective TRPV1 inhibitors and in TRPV1 $^{-/-}$ mice [45–47]. Capsaicin does not evoke cough in anesthetized animals, although it does evoke apnea [1, 48–50]. In conscious animals capsaicin evokes cough that is reduced by TRPV1 inhibitors [7, 30**, 51–53]. Similar data are observed in humans, where capsaicin produces cough bouts and urge-to-cough sensations [6, 11].

TRPV1 itself is a polymodal receptor that is activated by heat and extracellular acidity [44]. Airway C fibers are activated by acid, in a manner that is partially inhibited by TRPV1 inhibition/knockout [26, 47]. Consistent with these findings, TRPV1 inhibitors reduce citric acid-induced cough in conscious guinea pigs [51, 54, 55]. The other mechanism(s) underlying acid-induced activation of airway C fibers is probably mediated by ASIC channels [32*, 56].

TRP ankyrin 1 (TRPA1) is commonly co-expressed with TRPV1. TRPA1 is activated by a host of noxious stimuli including cinnamaldehyde, allyl isothiocyanate (AITC, pungent ingredient of wasabi), H₂O₂/ozone, cigarette smoke, dehydrated prostaglandins and products of lipid peroxidation and nitration [57–64]. This disparate group of substances all activate airway C fibers, in a manner that is abolished by inhibition or genetic knockout of TRPA1 [61, 64, 65]. Point mutation studies of TRPA1 suggest that a covalent modification of key intracellular cysteines by electrophilic moieties underlies much TRPA1's activation by these

activators [66, 67]. TRPA1 agonists evoke cough in conscious guinea pigs and humans, which is blocked by TRPA1 inhibitors [8, 9, 11, 30**, 68**].

TRPV1 and TRPA1 are also thought to contribute to nociceptor activation by GPCR ligands downstream of second messenger signaling [58, 69–71]. Bradykinin activates airway C fibers [18, 72], which is partially inhibited by TRPV1 inhibition/knockout [47, 73]. Other studies in dissociated nociceptive neurons suggest a role for TRPA1 in bradykinin-mediated responses [71, 74**]. In conscious animals bradykinin evokes cough [1, 75*], which is reduced by both TRPA1 and TRPV1 inhibitors [74**].

Both the nodose and the jugular vagal ganglia project C fibers to the airways [18, 24]. Jugular and nodose C fibers originate from different embryological sources [17], resulting in differential protein expression and function [18, 19, 24, 68**, 76, 77]. Nodose C fibers rarely express neuropeptides such as substance P and are activated by multiple stimuli including capsaicin, AITC, bradykinin, citric acid, α,β -methylene ATP ($P2X_{2/3}$), adenosine (A1 and A2A) and 2-methyl 5HT (5HT₃). Whereas jugular C fibers frequently express neuropeptides such as substance P and have a more limited range of stimuli sensitivity including capsaicin, AITC, bradykinin and citric acid. Jugular C fibers are not activated by α,β -methylene ATP, adenosine and 2-methyl 5HT due to a lack of specific receptor expression. Similarities in ligand sensitivity profiles [18, 38] suggest that afferent C fiber terminals accessible to stimulants injected into the pulmonary circulation (“pulmonary C fibers”) originate in the nodose ganglia. Whereas C fibers activated by stimulants injected into the bronchial/systemic circulation (“bronchial C fibers”) originate in the jugular ganglia.

Exposure of conscious guinea pigs to nebulized nodose C fiber-specific stimuli (e.g. ATP) failed to evoke cough [1, 30**]. This suggests that cough evoked by bradykinin, capsaicin or AITC is dependent solely on the activation of jugular C fibers. Such a hypothesis is supported by evidence that abolishing electrical activity using shRNA targeted to Na_v1.7 in nodose nerves has no effect on capsaicin-induced cough. Given that cough is abolished with either bilateral vagotomy or with complete shRNA knockdown of Na_v1.7 throughout the vagal ganglia [1, 31], it is reasonable to conclude that jugular C fibers are critical to cough triggered by C fiber stimulants.

Excitability changes in cough afferents

The transduction of graded potentials into action potential frequency depends on the electrical excitability of the afferent. In general, reducing K⁺ channel function and increasing Na_v function will increase excitability [16, 78], whereas reducing Na_v function and activating K⁺ channels may dampen airway afferent excitability [30**, 31, 79, 80**]. These changes in excitability are typically non-specific, i.e. they are independent of the ‘activating’ stimulus that produces the initial graded depolarization. Numerous inflammatory mediators, such as histamine, bradykinin and prostaglandins, have been shown to acutely increase nociceptor excitability [81–90]. Similarly, such mediators have been shown to increase the sensitivity of the cough reflex [83, 91–94]. Allergic inflammation has

been shown to increase the sensitivity of A δ fiber to punctate stimuli [25], although the mediators responsible for this effect are not known.

Cough afferent interactions

Central networks and mechanisms that regulate cough are beyond the scope of this review [95*, 96, 97*, 98, 99], but it is clear that cough mediated by nodose A δ fibers and jugular C fibers are differentially sensitive to anesthesia, thus suggesting major differences. Nevertheless, activation of airway jugular C fibers (with capsaicin or bradykinin) augments A δ fiber-mediated cough in anesthetized animals [50, 100]. This effect was mimicked by microinjection of capsaicin or substance P into the commissural nTS (airway C fiber central terminals) and prevented by microinjection of neurokinin antagonists [50, 101]. Esophageal C fibers also synapse in this area of the nTS and it is possible that activation of these nociceptors in the esophagus (e.g. acid) [102] may sensitize cough reflexes in similar ways [103].

Lung slowly adapting receptors are activated by mechanical forces during eupneic breathing and also by sustained positive end-expiratory pressure (PEEP). The role of these myelinated stretch receptors in modulating cough in anesthetized animals is perhaps species-specific: activity in SAR is permissive for cough in rabbits [104], inhibitory for cough in guinea pigs [3, 101] and has no effect on cough in humans [105].

Inhalation of nodose C fiber-specific stimulants (e.g. ATP) does not evoke cough in conscious animals. Indeed, it is thought that activation of pulmonary/nodose C fibers may inhibit cough elicited from the extrapulmonary airways in anesthetized animals [49](Y. L. Chou and B. J. Canning, unpublished observations).

Nasal inflammation has been shown to augment cough reflexes from the lower airways [106–108]. The nasal airways are innervated by trigeminal afferents, many of which are nociceptive (express TRPV1 and TRPA1) [60, 109–111]. Activation of nasal nociceptors with capsaicin or histamine failed to evoke cough [4, 5], but instead augmented cough sensitivity to vagal afferent stimulation [4, 112, 113]. Similar studies, however, with nasal TRPA1 agonists did not augment cough [114*]. Nasally-mediated cough augmentation was inhibited by intranasal treatment with the local anesthetic mesocain [113]. Convergence of capsaicin-sensitive trigeminal afferents with brainstem cough networks is suggested by c-fos staining in the nTS following intranasal capsaicin challenge [115].

TRP melastin 8 (TRPM8) is a menthol-sensitive cold receptor on a subpopulation of unmyelinated sensory neurons [116]. TRPM8 is found in both TRPV1+ and TRPV1-vagal and trigeminal neurons [111, 117**]. Nasal stimulation of TRPM8 with menthol, icilin or cold air profoundly decreased A δ fiber-mediated cough in anesthetized guinea pigs [117**, 118*], whereas TRPM8 stimulation in the trachea had no effect on cough sensitivity.

Afferent plasticity

Neural protein expression is not static, and inflammation/disease-induced changes in specific protein expression in cough afferents could have significant effects on cough. In

particular neurotrophins, which are produced within the airways are sites of inflammation and infection [119], are critical controllers of neuronal gene expression [120, 121]. De novo expression of neuropeptide substance P and CGRP in large diameter tracheal nodose neurons (presumed A δ fibers) were observed following allergic inflammation [122], infection with sendai virus [123] and nerve growth factor (NGF)-beta injections into the tracheal wall [124]. Given that substance P released from jugular C fibers in the nTS augments A δ fiber-mediated cough, it is reasonable to hypothesize that neuropeptides released centrally by the A δ fiber itself may also increase cough reflexes. In addition, de novo expression of the capsaicin receptor TRPV1 caused by allergic inflammation has been observed in myelinated airway afferents [125], including tracheal-specific nodose neurons [28**].

Afferent sensitivity to neurotrophins is determined by expression of specific tropomyosin-receptor kinase (Trk) receptors [126]: TrkA (activated by NGF), TrkB (activated by brain-derived neurotrophin factor (BDNF) and neurotrophin 4 (NT-4)) and TrkC (activated by NT-3). A recent study demonstrated that jugular C fibers preferentially expressed TrkA and nodose A δ fibers preferentially expressed TrkB [127]. As such it would be predicted that BDNF would have a greater impact on protein expression in nodose A δ fibers than NGF. Indeed, BDNF evoked substantial de novo TRPV1 expression in these nerves, whereas the effect of NGF was not significant [28**]. NGF-mediated neuropeptide expression in nodose neurons is consistent with the limited expression of TrkA in this population. TRPV1 expression was also induced by glial-derived neurotrophic factor (GDNF) [28**], which activates a family of receptors that are extensively expressed in airway afferents [127]. It is possible that de novo expression of TRPV1 (and perhaps other “C fiber” receptors) in the A δ fiber population indicates a switch of this fiber type to a more polymodal afferent. Thus it is plausible that A δ fibers (which stimulate cough even under anesthesia) in certain disease states could be activated by airway inflammation and inhaled irritants, thus potentiating cough.

Concluding Remarks

Anatomical, electrophysiological and pharmacological studies of multiple mammalian species indicate that there are two main afferent pathways that initiate cough: nodose A δ fibers in the extrapulmonary airways and airway jugular C fibers. Nodose A δ fibers respond to a limited range of stimuli that are consistent with a fundamental requirement to protect the airway from aspiration. Whereas jugular C fibers are adapted to respond to a host of stimuli associated with inflammation, infection and inhalation of irritants/pollutants. There is significant evidence that many airway afferent pathways interact within CNS networks to modulate cough (both positively and negatively). Furthermore, inflammation has been shown to produce both acute increases in afferent excitability and neuroplastic changes in afferent phenotype. Thus the tendency to cough in disease is likely modulated by a complex interaction of these many factors.

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Highlights

Distinct airway afferent subtypes have distinct activation profiles

Cough is evoked by stimulation of extrapulmonary A δ fibers in anesthetized animals

Cough is evoked by stimulation of jugular C fibers in conscious animals

Central interactions of multiple afferent pathways modulate the cough reflex

Inflammatory mediators alter afferent excitability and protein expression

Figure 1. The distribution and responsiveness of airway afferent subtypes in the guinea pig. RARs, rapidly adapting receptors; SARs, slowly adapting receptors. Taken from [5].

Figure 2.

Airway afferent subtypes have distinct sensitivities to various stimuli. A, representative recordings from tracheal afferents originating in the nodose ganglia (A δ fiber) and jugular ganglia (C fiber) of guinea pigs. Responses to capsaicin (1 μ M), 0.1M citric acid and von Frey fiber punctate mechanical force are shown. Adapted from [1]. B, representative recordings from afferents originating in the nodose ganglia (C fiber) and jugular ganglia (C fiber) innervating the guinea pig lung. Responses to ATP (30 μ M), α,β -methylene ATP (30 μ M) and capsaicin (0.3 μ M) are shown. Adapted from [18].

Figure 3. Distinct afferent subtypes mediate cough. A and B, the effect of in vivo knockdown of Nav1.7 in nodose neurons on (A) the cough evoked by punctate mechanical stimulation of the trachea in anesthetized guinea pigs, and (B) the cough evoked by inhalation of nebulized capsaicin (10 μ M) in conscious animals. The number of animals in each group is denoted in parentheses. C, Coughs evoked by various C fiber stimuli in conscious guinea pigs: saline (n=8), adenosine (10mM, n=6), 2-methyl-5HT (5mM, n=5), ATP (10mM, n=5), capsaicin (3 μ M, n=8) and AITC (10mM, n=5). Adapted from [30].

Figure 4.

Capsaicin-induced calcium responses in tracheal-specific nodose neurons in control and BDNF-treated guinea pigs. A: representative example of the Ca^{2+} responses, as measured by fura-2, in a tracheal-specific nodose neuron isolated from guinea pigs 2 wk following treatment with Matrigel alone (control, gray line) or treated with Matrigel containing 200 ng/ml BDNF (black line). Capsaicin ($1\mu\text{M}$) was applied for 60 s (black arrow). B:

percentage of tracheal-specific nodose neurons from control animals ($n = 4$ ganglia) and BDNF-treated animals ($n = 4$ ganglia) that responded to capsaicin. Taken from [28].

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